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Beta-Cell Replacement by Transplantation in Diabetes Mellitus: When Pancreas, When Islets, and How To Allocate the Pancreas?

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Abstract

A successful pancreas or islet transplantation produces an insulin-independent, euglycemic state that normalizes hemoglobin A1C levels for as long as the graft functions. Pancreas transplantation has been shown to definitely influence the progression of many secondary complications of diabetes. Islet transplants, even if they do not function well enough to induce insulin independence, still improve quality of life and reduce the frequency of hypoglycemic episodes in those with unawareness. Currently, approximately 1,300 pancreas transplants are performed annually in the USA, a frequency about 20-times that of islet allotransplants. The insulin-independence rates over time are definitely higher in the simultaneous pancreas/kidney transplantation category than in any islet recipient category. However, the insulin-independence rates are somewhat closer when comparing solitary pancreas transplants to recent islet transplant, a consequence of improved immunosuppression and islet isolation. Currently, five-year solitary pancreas graft survival rates are approximately 55% versus at best approximately 40% for islets. However, islet transplantation has a low morbidity and thus remains attractive as a minimally invasive procedure. For widespread application it needs to be made more efficient. The attrition of viable islets during isolation and engraftment is the main problem. The failure to obtain a high yield of viable islets from some donor pancreases creates the need to use more than one donor to provide a sufficient beta-cell mass to achieve insulin-independence in many recipients. Efforts are being made to increase the efficiency of islet isolation and engraftment so islet transplantation can become the form of beta-cell replacement therapy used in the majority of candidates. A deceased donor pancreas allocation policy for beta-cell replacement should be designed to foster efficiency and access to the most candidates for pancreas or islet transplantation. Current United Network for Organ Sharing policy in the USA on pancreas and islet transplants reflects the efficiency and durability of pancreas transplants, so candidates for a whole organ are given preference for donors < 50 years old and with a body mass

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index < 30. The United Network for Organ Sharing is now in the process of revising pancreas allocation for both solid organ and islet transplantation. The new allocation system will reduce the geographic inequities related to pancreas utilization, access to transplantation, and how long the candidates wait. It will maximize capacity by improving the opportunity for pancreas and islet candidates to receive a transplant. It will enhance efficiency and minimize the complexity of implementing and maintaining the operational requirements of a new allocation system. However, no matter how much the deceased donor organ allocation system is refined, there will never be enough human pancreases to provide beta-cell replacement therapy for all who could benefit. To do so will require the use of xenografts or insulin-producing, expanded autologous or allogeneic cell lines. These new modalities hold great promise for clinical application because of the unlimited supply and modifiable or intrinsic potential to escape some of the immunological consequences that plague solid organ xenografts as well as conventional allogeneic beta-cell replacement therapies. **(Trends in Transplant. 2010;4:99-107)**

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Key words

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Hyperglycemia is the most important factor in the development and progression of secondary complications of diabetes. The Diabetes Control and Complication Trial (DCCT) demonstrated that the microvascular and possibly macrovascular complications of diabetes may be prevented by maintaining euglycemia[1,2]. This study gave further support to the application of beta-cell replacement as an alternative to exogenous insulin administration in efforts to achieve optimal glycemic control so that the progression of long-term complications can be altered without the risk of hypoglycemia. The only treatments other than intensive insulin therapy that can influence the progression of secondary complications is beta-cell replacement by either pancreas or islet transplantation. Since diabetes is not a rapidly fatal disease, and because transplant procedures require the patient to receive life-long immunosuppression, the results of islet or pancreas transplantation must be sufficiently efficacious and safe to warrant their application in place of standard medical management of the primary disease. Even though pancreas transplantation has a high success rate, it is associated with surgical morbidity. Pancreas transplantation is a proven therapeutic treatment option for diabetes and is superior to manual intensive insulin therapy with regard to the efficacy of achieving glycemic control and beneficial effects on diabetic secondary complications. Islet transplantation is an alternative method of beta-cell replacement therapy.

Currently, islet transplantation is an investigational procedure for highly selective cases. An obvious advantage of islet transplantation is that it is minimally invasive for the recipient, but logistically it is more difficult[3-5].

A successful pancreas or islet transplant produces a euglycemic, insulin-independent state that normalizes hemoglobin A1C levels for as long as the graft functions. Transplantation also has the added physiological properties of pro-insulin and C-peptide release, not possible with intensive insulin therapy[6]. Through improved metabolic control by pancreas transplantation, many secondary complications of diabetes, including diabetic

neuropathy[7], autonomic neuropathy-associated sudden death[8], and diabetic nephropathy, in both uremic and nonuremic patients[9,10], may be markedly improved. A successful pancreas transplant significantly improves quality of life[11] and life expectancy[12,13]. The effect of islet transplantation on secondary complications has not undergone as rigorous a study on secondary complications as pancreas transplantation, but preliminary studies suggest the same effect[14]. Islet transplantation improves quality of life and has a significant ameliorating effect on the frequency of episodes of hypoglycemia[15]. One prospective study showed that islet transplantation not only reduced HbA1c levels more than intensive medical therapy, but was also associated with less progression of retinopathy during three years of follow-up[16].

Approximately 1,300 pancreas transplants are performed annually in the USA, about 20-times more than islet allotransplants. Of the pancreas transplants, 65-70% involves a simultaneous pancreas and kidney (SPK) transplant for patients with type 1 diabetes and chronic renal failure. These individuals are excellent candidates for an SPK transplant from the same donor because the immunosuppressive medications that are needed are similar to those for a kidney transplant alone and the surgical risk of adding the pancreas is low. The benefits of adding a pancreas transplant to ameliorate diabetes are profound–transplantation saves lives[12,13,17]. Simultaneous islet/kidney transplants are rarely performed, in part because of difficult logistics and because a successful islet isolation occurs at best in 50% of cases.

The second category for pancreas and islet transplantation consists of patients with type 1 diabetes who have received a previous kidney transplant from either a living or deceased donor[18-20]. This pancreas after kidney transplant category accounts for approximately 20% of patients receiving pancreas transplants, while approximately 15% of islet transplantations are done after a kidney transplant. The important consideration is that of technical risk[21], since the risk of immunosuppression has already been assumed for both groups[22].

The third category for pancreas and islet transplantation is composed of non-uremic patients with type 1 diabetes[23]. Candidates are those in whom the risk of immunosuppression is judged to be less than the risk of remaining diabetic on exogenous insulin therapy. Most of the candidates for a pancreas transplant alone have extremely labile diabetes and have difficulty managing day-to-day, with frequent emergency room visits or inpatient hospitalizations for hypoglycemia or diabetes. Other patients have significant difficulty with hypoglycemic unawareness that results in unconsciousness without warning, need assistance from those around them, and never should be left alone. For select patients, this state can be a devastating problem that affects their employment and their ability to keep a driver's license and creates concern about lethal hypoglycemia while asleep, as well as imposing an emotional toll on family members. Pretransplant evaluation often incorporates an assessment of the Clarke Score[24] to semi-quantitatively determine the severity of hypoglycemic complications in an effort to more fully understand the risk/benefit relationship for undergoing a pancreas or islet transplantation. Only about 15% of pancreas transplants are performed for this scenario (because so many pancreas transplants are done in renal allograft recipients who are already obligated to immunosuppression and thus the indications for beta-cell replacement are much more liberal), whereas for islet transplant, it accounts for about 85% of cases since almost all to date are in nonrenal allograft recipients.

The outcomes currently favor pancreas transplants in the SPK transplant group over any islet group. However, the results are much closer when solitary pancreas transplants are compared to islet transplants as immunosuppression

protocols have improved for islet transplantation. Currently, five-year solitary pancreas graft survival rates are approximately 55% in this group and at best approximately 40% for islets[25].

Importantly, islet transplantation has a low morbidity. Unfortunately, it is also inefficient because of the attrition of viable islets during isolation and engraftment. This problem results in failed attempts to obtain a sufficient yield of islets for transplants from some donor pancreases, and creates the need for more than one donor (retransplantation) to achieve a sufficient beta-cell mass in many recipients. Ideally, beta-cell replacement should be done by the least invasive means possible. However, if one is to maximize the number of recipients in the face of a scarce resource, deceased donor organ allocation for pancreas and islet allotransplantation has to be integrated in a way that balances the two objectives: treating as many as possible and minimizing morbidity[26].

The decision as to whether a beta-cell replacement candidate should receive an immediately vascularized solitary pancreas graft or an injection of isolated islets can be dictated, in part, by recipient characteristics[27], to circumvent the limitations of islet graft inefficiency. Exogenous insulin requirements are a rough guide to the number of beta-cells required to induce insulin-independence; the lower the requirement, the fewer islets that will be needed. Thus, beta-cell replacement candidates with high insulin requirements would be better suited for a pancreas transplant, while those with low insulin requirements might get by with a single-donor islet transplant.

A deceased donor pancreas allocation policy for beta-cell replacement should be designed to foster efficiency, and thus minimize the use of multiple islet donors (euphemism for retransplantation) for a single recipient. In the USA, organ allocation policies are set by the United Network for Organ Sharing (UNOS). The current pancreas allocation is complicated by the need for two lists: one for those only in need of beta-cell replacement, and one for those who also need a kidney. Currently, the priority varies according to the policies of local organ procurement organizations. In some organizations, uremic diabetic patients waiting for a kidney/pancreas transplant have no priority over uremic patients waiting for a kidney alone; a kidney/pancreas is allocated only when a uremic diabetic is at the top of the list. In other organ procurement organizations, the highest ranked uremic diabetic gets priority for a kidney/pancreas, no matter what the rank; in others, however, a level of rank is specified above which the highest ranked kidney/pancreas gets priority. In all organ procurement organizations, if no kidney/pancreas candidate is ranked high enough for an offer of both organs, the pancreas is offered to the highest ranked candidate for solitary pancreas or islet transplantation.

In regard to UNOS policy on pancreas and islet transplants, organs from donors < 50 years old are first offered to pancreas candidates, and those from donors > 50 first to islet candidates, primarily because intact pancreas transplants from donors over 50 years of age have increased technical complication rates at most pancreas programs. Pancreases from obese donors (BMI > 30) are also preferentially for islets, both because of the increased technical complication rate with pancreas transplants from such donors and the fact that the absolute number of islets isolated is proportional to donor size[28]. We know that nondiabetic, obese individuals have more islets than lean individuals because the beta-cell mass increases to cope with the increased insulin needs associated with obesity. This means that pancreases from obese donors could be assigned preferentially to recipients suitable to receive islet transplants because of their low insulin requirements, while pancreases from lean donors would be used for whole pancreas transplants to recipients with high insulin requirements.

Currently, UNOS is in the process of designing the pancreas allocation for both solid organ and islet transplantation[29]. UNOS is interested in a new national pancreas allocation system that will better address the needs of patients with diabetes with and without concurrent renal failure. There are several concerns with the way pancreases are currently allocated. First, there is no nationally established allocation practice for patients with diabetes and renal failure. Current pancreas allocation policy allows organ procurement organizations several choices on pancreas (pancreas alone) allocation practice. The candidates can be listed on separate or combined SPK/pancreas-alone waiting lists. The kidney may be allocated to SPK candidates based upon the kidney/pancreas match run, the kidney-alone match run, or a combination of match runs. Consequently, waiting times for SPK transplants vary widely across the country because of local or regional allocation decisions. Furthermore, current practice does not seek to maximize the utilization of the pancreas. Simultaneous pancreas and kidney transplants receive offers after other renal/extrarenal multiorgan transplants, kidney paybacks, and zero mismatch kidney-alone candidates. This allocation order leads to discarding of grafts that would likely be used if offered in the context of SPK transplantation but are declined for pancreas-alone transplants. Under the current system, 66% of pancreases are used for SPK transplant candidates. However, there are no specific listing criteria for SPK transplants with respect to the degree of pancreas dysfunction necessary to qualify to receive waiting time for an SPK transplant, it is only the criteria for a kidney that is used: glomerular filtration rate (GFR) or creatinine clearance (CrCl) of 20 ml/min or less.

A revised system is needed to improve the current pancreas allocation process. It should be consistent with the Organ Procurement Transplantation Network's long-range strategic goals and priorities: geographic equity in access and waiting time to deceased donor organs for transplantation; maximizing capacity of deceased donor organ transplantation; achieving operational efficiency and cost-effectiveness in implementing and maintaining the organ allocation system.

Depending on where a transplant candidate lives, some candidates may have to wait longer than others for a pancreas transplant. The first goal of the proposed pancreas allocation system reduces the geographic inequities related to deceased donor pancreas utilization, access to transplantation, and how long the candidates wait. Accomplishing these goals would mean instituting a consistent national system. Under this system, if a diabetic, uremic candidate on the list for an SPK transplant is allocated a pancreas from a local deceased donor and accepts it, then that candidate would also receive a kidney from the same deceased donor.

The second goal is to maximize capacity by improving the opportunity for pancreas candidates to receive a transplant. This would be accomplished by combining SPK and pancreas-alone candidates onto a single match run list. On a single list, candidates for both categories of pancreas transplants would have an equal opportunity to receive offers of high quality organs. A single list for all pancreas candidates would be operationally efficient for organ procurement organizations. It would also retain some high quality kidneys for the kidney allocation system in the situations in which a pancreas graft is allocated for pancreas-alone transplantation. Right now, diabetic, uremic candidates are not fully incentivized to receive a kidney from a living donor if they will subsequently be put on a wait list for a solitary pancreas in a donation service area that allocates organs to SPK candidates before allocating them to pancreas-alone candidates. In this situation, if a candidate chooses to take a living donor kidney and then wait on the list for a pancreas, that

candidate would receive a local pancreas offer only if all the local SPK candidates had turned down that pancreas. This process results in additional waiting time for pancreas after kidney transplantation compared to declining a living donor kidney and continuing to wait for the SPK transplant. Also, in many circumstances these pancreases that are refused by all the SPK candidates are of lower quality than the pancreases the candidate would be able to receive if he or she had waited for an SPK rather than taking the living donor kidney. This situation might discourage candidates who need both a kidney and a pancreas from taking a living donor kidney followed by a deceased donor pancreas. The proposed allocation change would mean that candidates may be more inclined to accept a kidney from a living donor, knowing they subsequently will get a good quality solitary pancreas offer.

On the other hand, for pancreas transplant programs that readily accept regional and national solitary pancreas offers, the waiting time for a pancreas after kidney transplant may be relatively short. Thus, in these programs or donation service areas, a living donor kidney followed by a solitary deceased donor pancreas transplantation can actually reduce the time of being both dialysis-free and insulin-independent for uremic diabetics over those on the SPK waiting list. Thus, the value on survival of preempting dialysis with a living donor kidney transplant offsets the negative aspects of waiting for a solitary pancreas transplant and having two operations[18-20]. And of course, there is the option of a living donor SPK transplant[30,31].

The third goal is to enhance efficiency and minimize the complexity of implementing and maintaining the operational requirements of a new pancreas allocation system. The proposed method would allocate deceased donor pancreases separately from the current kidney allocation system. This method would effectively disentangle the system of a pancreas allocation from kidney allocation. There appears to be enough deceased donor kidneys (both standard and expanded criteria) available to accommodate this allocation change without adversely affecting pediatric or adult kidney transplant activity. Importantly, this process would result in a faster and more efficient method of allocating organs. It would also be less costly to implement and maintain.

The fourth goal is to optimize pancreas transplant access without adversely affecting kidney transplantation. Specifically, a new pancreas allocation system would not affect transplant volume for adult and pediatric kidney recipients as well as ethnicity, age, and gender of recipients. This goal would be accomplished by instituting objective medical qualifying criteria relating to renal dysfunction and diabetes for SPK candidates. These candidates would be eligible to accrue SPK waiting time only if they meet qualifying criteria based on renal and metabolic function. The kidney function criteria for qualifying includes either being on dialysis, having a GFR or CrCl $\leq$ 20 ml/min. Qualifying pancreas function criteria includes either being on insulin and having a C-peptide value $\leq$ 2 ng/ml or being on insulin with glycemic intolerance with a C-peptide value > 2 ng/ml and a body mass index (BMI) $\leq$ 30 kg/m^2. In addition, a single list for all pancreas transplant candidates would retain some high quality kidneys for the kidney allocation system. Finally, the proposal includes a system to monitor allocation of standard criteria deceased donor kidneys for pediatric and adult kidney alone recipients and SPK recipients with respect to donor ages $\leq$ 35 and > 35 years. It should be noted that pancreas transplantation is effective in inducing insulin-independence in diabetic patients (including type 2), regardless of the presence or absence of C-peptide or the levels[32]; nevertheless, C-peptide is being used in the policy formulations.

Advances are being made in the isolation of islets to increase the proportion of islets

that remain viable for transplantation; for example, the use of agents that prevent apoptosis after isolation[33]. As these advances are applied clinically, the insulin requirement threshold below which a single-donor islet transplant would be sufficient to induce insulin independence could be raised, increasing the proportion of beta-cell replacements done by the minimally invasive technique. Conversely, the BMI requirements to be an islet donor could be progressively lowered as the islet isolation efficiency increases in terms of viability. Ultimately, such improvements would result in a fully integrated list of pancreas and islet candidates, each being able to accept nearly all donors regardless of characteristics, and most beta-cell replacement therapy would be done by islet transplantation. We are, of course, not at that point yet.

Besides improving the efficiency of islet isolation, other alterations in strategies may allow a lower number of isolated islets to induce insulin-independence in recipients than is currently the case, for example, using a truly non-diabetogenic immunosuppressive regime (even the Edmonton protocol is diabetogenic with its inclusion of a calcineurin inhibitor). In many pancreas transplant programs, the immunosuppressive regimen is free of steroids[22,34].

By combining several aspects of the recipient and donor selection criteria, technical improvements in islet isolation and immunosuppressant selection, as outlined above, has allowed insulin independence to be achieved with islets from a single donor[35]. There are several recent reviews on islet transplantation that show the promise of islet transplantation to eventually be the nearly sole method of beta-cell replacement therapy[14,36,37]. However, to be truly a treatment for all diabetics, an unlimited source of islets is needed, and this could only be met by islet xenotransplantation, as recently reviewed[38], or through development of glucose-responsive, insulin-producing expanded cell line.

If one deceased donor pancreas could consistently yield enough islets to induce insulin independence in a diabetic recipient, regardless of donor characteristics or recipient's exogenous insulin requirements, islet transplantation would largely replace pancreas transplantation. An exception would be candidates who also have exocrine deficiency, for example, those who became diabetic as a result of pancreatectomy for benign disease[39]. Islet autotransplantation performed at the time of pancreatectomy for chronic pancreatitis can preserve insulin independence in some patients[40,41], but for those in whom it does not, or in whom it was never attempted, it makes sense to transplant a pancreas (rather than simply islets) with enteric drainage of the exocrine secretions so that normal intestinal absorption can also be restored[39].

The shortage of deceased donors for those in need of organ replacement therapy of all kinds has led to the use of living donors, including for the pancreas. Segmental pancreas transplants from living donors have been done since 1979 at the University of Minnesota[31], and this institution had an even earlier experience with two cases of islet allografts from living donors[42]. In countries where deceased organ donors are in even shorter supply, the incentive to use living donors is particularly strong. For example, in Japan the number of living donor liver transplants greatly exceeds that from deceased donors, and the transplant group in Kyoto also did a living donor islet transplantation a few years ago[43,44]. However, it is unlikely that the use of both deceased and living donors can meet the demand for beta-cell replacement therapy any better than it has for any other organ, even in countries with relatively high numbers of both types. Thus, in the long term, either islet xenografts or induction of endogenous beta-cell regeneration will be the answer[26,38].

Meanwhile, we must use the resource at hand: a limited number of allogeneic donor

pancreases for beta-cell replacement therapy. To answer the questions posed in the title, beta-cell replacement therapy should be done in insulin-dependent diabetic patients who are either obligated to immunosuppression (nearly all diabetic renal allograft recipients should be candidates) or in those whose problems with achieving sufficient metabolic control of diabetes using exogenous insulin (primarily those with hypoglycemic unawareness) exceed the potential side effects of immunosuppression. For candidates in whom the insulin requirements are low enough so that islets isolated from a single donor would predictably induce insulin independence, perform an islet transplant; in those whose requirements are so high that more than one donor would be needed for the islet approach, and who are not at high risk for surgical complications, carry out a pancreas transplant. If the surgical risk is unacceptable in high insulin-requiring candidates, then perform an islet transplant, with the exception that islet retransplantation can be done over time to eventually achieve insulin independence. With this approach, beta-cell replacement can be done in the most patients with the highest insulin-independent rate possible, while allowing minimally invasive surgery to be done in some candidates at no expense to those who require more (a solid organ).

Finally, a word about the mortality risk of beta-cell replacement therapy versus remaining on insulin for a diabetic patient. The mortality risk of pancreas transplantation, in absolute terms, is very low, with patient survival rates at one year ranging from 95 to 98% in all three (simultaneous pancreas/kidney, pancreas after kidney, pancreas alone) recipient categories[45]. However, Venstrom, et al., in an analysis of UNOS data from 1995 through 2000, found that the posttransplant mortality rate of solitary pancreas transplant recipients (pancreas alone or pancreas after kidney transplant) was higher than for candidates who remained on the waiting list[46]. Analyses of this type are very difficult to perform, and in a separate analysis by Gruessner, et al.[47], but this time counting patients only once that were multiply listed or changed centers, the mortality rate for solitary pancreas transplant recipients was not higher than for wait-listed patients.

Thus, it appears that pancreas transplantation and exogenous insulin treatment are at least equal in survival probabilities for the diabetic patients accepted as transplant candidates. As reviewed by Robertson[48], every study that has been done on quality of life favors pancreas transplantation over exogenous insulin for such patients, most of whom have significant problems with the latter (such as hypoglycemic unawareness). What is needed now is to increase the efficiency of islet isolation and engraftment so beta-cell replacement therapy can be done by the minimally invasive technique in the majority, rather than the minority, of candidates.

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47. Gruessner RD, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant. 2004;4:2018-26. **This article and the one preceding both definitively show the great beneficial effect of kidney-pancreas transplant on survival of uremic diabetics over those who remain on the wait list. What is controversial is whether the mortality risk of a solitary pancreas transplant exceeds that of not being transplanted and in the article by Gruessner, et al. the answer is no.*
48. Robertson RP. Impact of pancreas and islet transplantation on acute and chronic complications of diabetes. Curr Opin Organ Transplant. 2005;10:95-9.

Suggested Readings

Sutherland DER. Beta-cell replacement by transplantation in diabetes mellitus: which patients at what risk, which way (when pancreas, when islets), and how to allocate deceased donor pancreases. Curr Opin Organ Transplant. 2005;10:147-9. **This issue has several articles, besides the one cited, on all aspects of pancreas and islet transplantation. The article cited has formed the basis of the current discussion adding Dr. Kaufman's perspective as current Chairman of the UNOS Pancreas Allocation Committee.*